REMARKS/ARGUMENTS

Claim Objections

Spelling corrections are provided in amendments to claims 16, 23, and 35. Entry is respectfully requested.

Claim Rejections under 35 USC 112, first and second paragraphs

The Office Action mailed May 20, 2005 rejected claims 23-26 and 28-35 under 35 USC 112, second paragraph as allegedly indefinite.

The Office Action stated that claims 23-24 are indefinite because "it is unclear to what or who the PLGF-1 is being administered to." Without conceding to the correctness of this rejection, Applicant amends claims 23-24 herein to include "to adult individuals" after "administering." The administration to adult individuals is supported in Example 7 of the specification. It is further noted that the claimed cosmetic treatment of natural skin aging and natural loss of hair, as supported in the specification, should implicitly and unambiguously identify the recipient of the treatment, that is, "human".

Reconsideration and withdrawal of these rejections, including for dependent claims 25-26 and 28-29, are respectfully requested.

The Office action also rejected claims 30 and 31. Claims 30 and 31 are amended to identify that PLGF-1 is type 1 Placental Growth Factor. Reconsideration and withdrawal of the rejections based on this issue are respectfully requested.

The Office action stated that claims 32-33 are rejected, apparently based on the assertions that, "an emulsion of water/oil or of oil/water will still create the same composition, therefore it is unclear what the distinction between a W/O emulsion versus a [sic] O/W emulsion is." As to this rejection, the person skilled in the field of pharmaceutical technology knows that there are at least two types of emulsion: W/O (water-in-oil) and O/W (oil-in-water) emulsions. Their properties are deeply different based on which phase is external. W/O means that the external phase of the emulsion is an oily phase, while the dispersed phase is an aqueous phase. This emulsion is essentially lipophylic. On the other hand, O/W means that the external phase of the emulsion is an aqueous phase, while the dispersed phase is an oily liquid. This emulsion is essentially hydrophilic. Accordingly, two compositions consisting of either W/O or O/W emulsion cannot be the "same composition" as maintained by the Examiner, since they exhibit different adsorption and bioavailability properties. Such differences may hold true for other forms of pharamaceutical compositions, for example an aqueous solution and a lipid-based cream. These nonetheless belong in the art-recognized class of forms of pharmaceutical compositions (or cosmetic compositions).

Reconsideration and withdrawal of these rejections, including for dependent claims 34-35, are respectfully requested.

Rejections under 35 USC 102

Claims 16-22, 27, and 30-35 stand rejected under 35 USC 102, as being anticipated by Ziche et al. (1997 Lab. Invest. 76(4) 517-531, hereinafter, "Ziche"). In part, the Office action states that Ziche teaches that PLGF-1 promotes angiogenesis in the avascular rabbit cornea, and compared this to claim 16, stating that "Claims 17-22, 27 are anticipated by Ziche because they are also just methods of using PLGF-1 comprising preparing a medicament that comprises PLGF-1 as an active principle."

However, claim 16 teaches more than just preparing a medicament that comprises PLGF-1 as an active principle. The wherein clause indicates the claim is directed to promotion of angiogenesis

in the treatment of a state selected from the group provided in claim 16. Although Ziche demonstrates angiogenesis under defined laboratory conditions in rabbit cornea and chick chorioallantoic membrane, Ziche is silent on use of PLGF-1 as a treatment for any condition, in contrast noting instead on page 517 that "Angiogenesis plays a major role in tumor progression. . . . and pilot studies suggest that detection of angiogenic factors in tumor specimens might become an important diagnostic tool." Arguably, this evidences a teaching away from use of PLGF-1 in treatment of pathological conditions. Further, Ziche is clearly silent on a treatment of any state as described in claim 16. Accordingly, Ziche does not anticipate claim 16 as it does not teach all limitations of claim 16.

More specifically, claim 16 is intended to protect the use of PLGF-1 for treating three specific groups of pathological states, all directly or indirectly relating to alterations of the connective tissues. These are (1) diseases and pathological alterations involving the cutaneous or subcutaneous connective tissues; (2) scleroderma; and (3) early skin aging. This therapeutic effect is achieved through an improved angiogenesis, which in itself is not the therapeutic effect, but the mechanism of action.

As correctly indicated by the Examiner, Ziche discloses the ability of PLGF-1 to elicit angiogenesis. Ziche demonstrates this in two animal models, namely in the rabbit cornea and in the chicken chorioallantoic membrane. However, as evident from the first line of the section "Discussion", this PLGF-1 property is simply a biological activity developed on normal (healthy) rabbit cornea or chorioallantoic membrane. This biological activity cannot be confused with a pharmacological, therapeutic effect that necessarily implies the capability of correcting and recovering an abnormal situation (in particular, here, one involving connective tissue alterations). This capability is not recognized nor enabled in Ziche's article, which as noted is completely silent on any envisageable therapeutic application of PLGF-1, let alone on the specific therapeutic treatment of the diseases cited in claim 16.

Further, the present application describes on page 6 under the heading "Diseases" the clinical picture accompanying the diseases cited in claim 16. This picture is characterized by fibroblast activation and excessive production and deposit of sclerosed collagen with formation of fibrosis and calcification zones. Neither Ziche nor any other cited document shows or suggests that this clinical situation is caused by or correlated to a deficient angiogenesis in the connective tissues. Nor could the skilled reader find any suggestion in Ziche's teaching that PLGF-1 would be able to improve vascularization in damaged sclerotic connective tissues, based on observations in healthy cornea or chorioallantoic membrane. More importantly, Ziche does not suggest that an improved vascularization, if any, would be able to restore the healthy state of the connective tissues.

Accordingly, the biological activities shown by Ziche are not suggested to have any involvements or cause/effect relationship with alterations of the connective tissue, nor effectiveness when used in a therapeutic composition..

Also with respect to claim 16, Ziche is not enabling disclosure, and therefore cannot anticipate the instant invention as claimed. It is well settled law that reference must be enabling in order to anticipate a claim. The Federal Circuit has stated in *In re Donahue*, 226 USPQ 619 (Fed. Cir. 1985) that:

> It is well settled that prior art under 35 U.S.C.§102 (b) must sufficiently describe the claimed invention to have placed the public in possession of it. *In re Sasse* 629 F.2d 675, 681, 207 U.S.P.Q. (BNA) 107, 111 (CCPA 1980); *In re Samour*, 571 F.2d at 562, 197 U.S.P.Q. at 4; see also *Reading & Bates Construction Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 651-52, 223 U.S.P.Q. (BNA) 1168, 1173 (Fed. Cir. 1984). Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention. See *In re LeGrice*, 301 F.2d at 939, 133 U.S.P.Q. at 373-75. Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. *In re Borst* 52 C.C.P.A. 1398, 345 F.2d 851,

855, 145 U.S.P.Q. (BNA) 554, 557 (1965), cert. denied, 382 U.S. 973, 83 S. Ct. 537, 15 L. Ed. 2d 465 (1966).

Thus, if a reference is non-enabling for a particular invention, it cannot anticipate that particular invention. Here, at a minimum, Ziche is silent on the method of use of a PLGF-1-containing medicament in the treatment of the states as indicated in claim 16. Based on this failure to teach and therefore enable, Ziche cannot properly be held to anticipate claim 16.

Reconsideration and withdrawal of this rejection, including for dependent claims 17-22 and 27, are respectfully requested.

Claims 30-35 stand rejected under 35 USC 102 as being anticipated by Ziche. In part, the Office action states that "regardless of the units of dosage recited by the claims, the Ziche et al. reference still meets the claim limitations [of claims 30-35] in that it teaches a pharmaceutical composition comprising PLGF-1 in the appropriate monomeric, dimeric, and trimeric forms." It is advanced, per below, that the dosage range is relevant to the novelty of the claim as a whole, and here provides a therapeutic dosage range not set forth by Ziche. Further, the Office action notes that the PlGF-1 protein of Ziche ". . . was approximately 0.17 mg/l of conditioned medium." However, Applicant notes for the record that this represents a back-calculation, following purification, to the approximate concentration in cultures containing the PlGF-1-producing recombinant cells (see pages 527-528). It is believed that, for the purposes of anticipation, the back-calculated concentration of PlGF-1 in a conditioned media obtained from a recombinant cell culture is not relevant to the present discussion of levels of PLGF-1 in, respectively, the pharmaceutical composition of claim 30 nor the cosmetic composition of claim 31.

Further, it is appreciated that claim 30 seeks protection for a pharmaceutical composition comprising PLGF-1, essentially in dimeric form, as active principle in an amount of 50 micrograms to 30 milligrams per parenteral unit dose or 0.1 to 10 milligrams per gram of topical

composition. In contrast, as elucidated below, Ziche discloses the use of the purified PLGF-1 in amounts completely different from those of the present invention, and such usage amounts of Ziche are not considered therapeutic doses.

The amount of the active principle is the second essential characteristic of any medicament, the first being the principle itself. As evident from the sections "*PGF-1 Promotes Angiogenesis in ARC*" on page 518, or "*PGF-1 Promotes Angiogenesis in Embryonic CAM*" on page 519, or "*Chemotactic Effect*" on page 521, the Ziche document discloses compositions in the forms of implants or solutions comprising no more that 200 ng/pellet (i.e. dosage-unit) or 100 ng/ml solution.

On the contrary, the composition of claims 30 comprises amounts of active agent, which vary from 50 μg ($5x10^4$ ng) to 30 mg ($3x10^7$ ng) per unitary dose of parenteral composition, and from 0.1 mg (10^5 ng) to 10 mg (10^7 ng) per gram of topical composition. The meaning of "parenteral unit dose" is very clear for the skilled person that is aware that the volume to be given in one single injection, thus normally the volume of a vial, is roughly in the order of milliliters or less. Thus, the highest amounts disclosed by Ziche ($2x10^2$ ng/pellet or $1.8x10^2$ ng/ml) are substantially lower (at least by a factor of 100) than the amounts defined in claim 30. Also, assuming arguendo that the back-calculated concentration of 0.17 mg/l were relevant, this is substantially lower than a parenteral dose of 50 μg in a several millilter dose (i.e., 0.17 mg/l = 0.17 μg/ml, which remains far below 10 μg (an extreme example, if the 50 μg were in a 5 ml dose)). Therefore, the concentrations and levels used by Ziche do not fall within the claimed ranges, Ziche does not teach nor suggest the substantially higher levels of claim 30, and Ziche cannot properly be considered to anticipate claim 30.

The same applies to claim 31, which seeks protection for a cosmetic composition comprising from 0.01 mg (10^4 ng) to 0.09 mg ($9x10^4$ ng) per gram of composition.

Accordingly, reconsideration and withdrawal of the rejections of claims 30 and 31, and dependent claims 32-35, are respectfully requested.

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

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The Examiner is invited to call the undersigned if clarification is needed on any aspects of this Reply/Amendment, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion. In particular, if amendment of a claim, including alteration of a claim style to a style more commonly found in U.S. patent applications, may be viewed to advance this application to allowance status, the courtesy of a telephone call to the undersigned toward such amendment will be most appreciated.

Respectfully submitted,

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